IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of: Wedeking et al.

Title: METAL COMPLEXES DERIVATIZED WITH FOLATE FOR USE IN DIAGNOSTIC AND THERAPEUTIC APPLICATIONS

Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT
PURSUANT TO 37 CFR 1.97 and 1.98

Dear Sir:

In accordance with the suggested procedure of 37 CFR 1.97 and 1.98, Applicants are submitting herewith copies of all of the prior art references identified on the enclosed list, which are considered to comprise the closest prior art of which the undersigned attorney, the inventors and anyone else believed to have been substantially involved in the preparation of this application are aware. Each of these references will be discussed below in a brief paragraph.

Diagnostic and therapeutic compositions in the form of a complex for enhancing transmembrane transport of a diagnostic or therapeutic agent. The complex contains the α, γ and bis isomers of the folate receptor-binding analogs of folate; a metal chelated by a ligand, and in one embodiment, a chemotherapeutic agent.

1. U.S. Patent No. 5,416,016, issued to Low et al. on May 16,1995, is directed to a method for enhancing transmembrane transport of exogeneous molecules comprising: contacting a membrane of a living cell with a complex formed between the exogenous molecules and ligands selected from biotin, biotin analogs, and/or folic acid and folate analogs to initiate receptor mediated transmembrane transport of the ligand complex.

The exogenous molecules include a large variety of compounds, peptides, proteins and nucleic acids, such as enzymes, analgesics, antihypertensive agents, antiviral agents, antihistamines, cancer drugs, H-2 antagonists, expectorants, vitamins, plasmides and the like.

Included in the listing of exogenous molecules are "diagnostic agents".

There is no teaching or suggestion as to what diagnostic agents can be used or how they are or can be complexed with the ligands. There is also no disclosure as to how the ligand-diagnostic agent functions in a method of diagnosis.

2. WO 96/36367, published Nov. 21,1996, relates to a composition and method for tumor imaging. The composition comprises biotin or biotin receptor-binding analogs of biotin, folate or folate receptor-binding analogs of folate complexed with a diagnostic agent.

The publication also discloses a large variety of pharmaceutically active compounds which can be complexed with the biotin or folate ligands.

The publication broadly states, but without sufficient specifics, that any diagnostic agent can be used in conjunction with the ligands, such as radiopharmaceuticals. Radionuclides specifically mentioned are: radioisotopes of gallium, indium, copper, technetium and rhenium.

The publication distinguishes between the two isomers of DF-folates, i.e. the α and the γ-carboxyl folates. The affinities of the two folate isomers for cell surface folate receptors are stated as follows (p. 49, lines 3-7) "A 50% decrease in bound, [^{3}H] folic acid was observed in the presence of an equimolar amount of the DF-folate (γ) conjugate, while the DF-folate (α) conjugate display no ability to compete with the radiolabeled vitamin."

In summary, the publication discloses that the α - conjugate is inable to compete with free folate for the cell surface receptor. For this reason, the "active" γ-linked isomer was separated from the "inactive" γ-linked isomer when the In-DTPA-folate conjugate was synthesized in Example 34 (p.61).

It is apparent that the publication teaches the use of the γ-folate isomer in conjunction with the radionuclides of gallium, indium, copper, technetium and rhenium. It does not teach γ-folate in conjunction with paramagnetic contrast agents complexed with macrocycles, and it teaches away from the use of α-folate in combination with active agents.

3. U.S. Patent No. 5,248,492, issued to Groman et al. on Sept. 28, 1993, relates to the stabilization of supermagnetic colloids with low molecular weight carbohydrates, such as mannitol, sorbitol, and maltose.

4. U.S. Patent No. 5,055,288, issued to Lewis et al. on Oct. 8, 1991, relates to biodegradable supermagnetic metal oxides, such as iron oxide crystals. The contrast agents are associated with macromolecular species which have a molecular weight in excess of 1 kilodalton.

5. U.S. Patent No. 5,314,679 is a divisional of U.S. Patent No. 5,055,288 and discloses the same subject.

6. U.S. Patent No. 5,352,432, issued to Menz et al. on Oct. 4, 1994, relates to NMR contrast agents comprising: biodegradable supermagnetic metal oxides associated with macromolecular species, such as proteins, hormones and polysaccharides. The MR contrast agents in association with the macromolecules are capable of undergoing receptor mediated endocytosis.

No combination of folates with chelated paramagnetic species are disclosed.

7. U.S. Patent No. 5,069,216, issued to Groman et al. on Dec. 3, 1991, relates to biologically degradable superparamagnetic metal oxides as MR contrast agents. The metal oxide particles may be coated with a polysaccharide, a protein or a polypeptide.

8. WO 92/11037 relates to a method for the targeting of a therapeutic agent to cells, wherein a complex is formed between a therapeutic agent and a polysaccharide capable of reacting with a cell receptor, and wherein the resulting complex is internalized into the cell by receptor mediated endocytosis. In one embodiment, a complex of a therapeutic agent containing iron and the polysaccharide arabinolactan is formed and used to deliver iron to hepatocytes by RME.

9. WO 90/01899 discloses biodegradable supermagnetic MR imaging contrast agents comprising aggregates of iron oxide crystals associated with macromolecular species.

10. U.S. Patent No. 5,373,093, issued to Vallarino et al. on Dec. 13, 1994, discloses macrocyclic complexes of lanthanides, actinide and yttrium ions suitable for magnetic resonance imaging.

11. U.S. Patent No. 5,399,338, issued to Born et al. on March 21, 1995, relates to biomodulators in conjunction with antibodies which are linked to imaging-active moieties.

12. U.S. Patent No. 5,336,506, issued to Josephson et al. on Aug. 9, 1994, discloses a complex formed between a therapeutic agent and a polysaccharide capable of interacting with a cell receptor, which on administration to a host, is internalized into the cell by receptor mediated endocytocis. (RME)

13. U.S. Patent No. 5,478,576, issued to Jung et al. on Dec. 26, 1995, relates to arabinogalactans as carriers for delivering therapeutic agents to cell receptors capable of receptor mediated endocytosis (RME).

14. U.S. Patent No. 5,262,176, issued to Palmacci et al. on Nov. 16, 1993, relates to a synthesis of colloidal metal oxide coated with a polymer. The polymer may be a polysaccharide.

15. U.S. Patent No. 5,141,739, issued to Jung et al. on Aug. 25, 1992, discloses a method for targeting an x-ray contrast agent to cells or organs using a complex of a radioprague label with a saccharide capable of interacting with a cell receptor. The resulting complex may then be internalized into the specific proportion of cells or organs by receptor mediated endocytosis.

16. U.S. Patent No. 5,108,921, issued to Low et al. on Apr. 28, 1992, is directed to a method comprising contacting a membrane of a living cell with a complex formed between an exogenous molecule and a ligand selected from biotin/analogs and/or folic acid/analogs to initiate receptor mediated transmembrane transport. The exogenous molecule can be a peptide, a protein or a nucleic acid.

17. U.S. Patent No. 5,284,646, issued to Menz et al on Feb. 8, 1994, discloses biodegradable supermagnetic metal oxide associated with macromolecular species, such as hormones and polysaccharides, for use as MR contrast agent.

18. WO 90/01295, published on Feb. 22, 1990, is directed to MR contrast agents whose action is based on receptor mediated endocytosis. The contrast agents are biodegradable supermagnetic metal oxides associated with macromolecular species including serum proteins, hormones and polysaccharides.

19. U.S. Patent No. 5,358,704, issued to Desreux et al. on Oct. 25, 1994, discloses tetraazacyclododecane macrocycles containing a fused cyclohexyl ring as metal-chelating ligands; in the form of metal complexes containing paramagnetic metals the invention is used for MR imaging.

20. WO 96/11712, published on Apr. 25, 1996, discloses a delivery vehicle which is capable of bounding to and taken into target cells delivering paramagnetic ions for MR imaging of the cells. The deliver vehicle comprises a polymeric molecule having a net positive charge complexed with another polymeric molecule having a net negative charge.

21. WO 90/01900, published on March 8, 1990, relates to carrier system for enhancement of magnetic resonance imaging. The system consists of three principal components:

1) a ligand, such as a glycoprotein;
2) a paramagnetic substance; and
3) a complexing or chelating agent, such as diethylenetriamine pentaacetic acid (DPTA

22. WO 96/11023, published on Apr. 18, 1996, discloses liposomes bound to a chelated diagnostic agent, the chelating agent having a macrocycle chelant moiety.

23. U.S. Patent No. 5,342,606, issued to Sherry et al. on Aug. 30, 1994, discloses polyazamacrocyclic compounds for complexation of metal ions including

1,5,9 - triazacylododecane,

1,4,8,12 - tetraazacyclopentadodecane

1,4,8,11 - tetraazacylotetradecane.

24. WO 91/07911, published on June 13, 1991, discloses polyphosphonate ligands combined with paramagnetic metal cations for MRI.

25. U.S. Patent No. 4,639,365, issued to A.D. Sherry on Jan. 27, 1987, discloses chelates of gadolinium with

1,4,7 - triazacyclononane - N,N',N'' - tiracetate,
1,4,7,10 - tetrazacyclododecane - N,N',N''' - tetraacetate, and
1,5,9, - triazacyclododecane - N,N',N'' - triacetate for use as NMR contrast agents.

None of the references alone or in combination teach or suggest the present invention; Applicants believe that the invention is novel and unobvious.

Respectfully submitted,

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